structure of which was unambiguously established by X-ray diffraction analysis of the derived *p*-bromobenzoate **15b** (Figure 4). As expected, osmylation took place from the less hindered face. Oxidative cleavage using sodium periodate followed by sodium borohydride reduction and acidic workup produces the desired spiroketal **14b**, accompanied by ~5% of the axial isomer. The overall yield for the synthesis of **14b**, starting from the ortholactone, is 63%. An identical route was followed to prepare the lower homologue **14a** in a respectable 54% overall yield.

In summary, we have shown that the ISMS reaction is a powerful tool for the production of tetrahydropyrans, spiroethers, and spiroketals. These are important subunits in a variety of natural products. By using the ISMS annelation, the spiroketals **14a** and **14b** were synthesized readily and in high overall yields. Further work on expanding the scope of this novel methodology as well as on its application to the total synthesis of milbemycin β3 and okadaic acid is being actively pursued in this laboratory and will be reported in due course.

Acknowledgment. Financial support for this work by the Algerian Ministry for Higher Education is gratefully acknowledged. Awards from the Science and Engineering Research Council, The Nuffield Foundation, and The Royal Society are highly appreciated. We are grateful to P. R. Ashton and I. R. Johnstone (MS), S. J. Thorpe (GC), and Dr. B. F. Taylor (NMR) for their enthusiastic contribution.

Supplementary Material Available: Experimental details for obtained compounds (13 pages). Ordering information is given on any current masthead page.

Intramolecular Oxypalladation and Cross-Coupling of Acetylenic Alkoxides

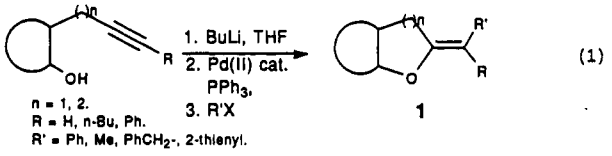
Fen-Tair Luo,* Inessa Schreuder, and Ren-Tzong Wang

Institute of Chemistry, Academia Sinica, Taipei, Taiwan, Republic of China

Received February 5, 1992

Summary: Stereodefined 2-alkylidenetetrahydrofurans and pyrans were synthesized by treatment of alkyl or aryl acetylenic alcohols with *n*-BuLi in THF at 0 °C followed by addition of a solution of 10 mol % of $Pd(OAc)_2$ or $PdCl_2$ and PPh_3 in THF and 1 equiv of an organic halide.

The construction of acid-sensitive exocyclic alkenes 1 with ≥98% stereoselectivity is a synthetic challenge.[1] Our interest in the palladium-catalyzed cyclization and cross-coupling of acetylenic aryl halides[2] or triflates[3] encouraged us to examine analogous acetylenic alcohols for the synthesis of such alkenes. The palladium-catalyzed cyclization of acetylenic alcohols has been shown to be an efficient route to the synthesis of various heterocycles.[4] However, the stereoselective synthesis of alkenes 1 from acetylenic alcohols via palladium catalysis is still essentially unexplored.[5] We now report a new strategy for the stereoselective construction of alkenes 1 via the palladium-catalyzed cyclization and cross-coupling of acetylenic alcohols with organic halides (eq 1).



(1)

Our results (Table I) demonstrate that a wide range of stereodefined α-alkylidene cyclic ethers can be formed through this cyclization and coupling reaction. A typical procedure is as follows. A solution of *n*-BuLi (1.4 mL of 1.6 M in benzene, 2.2 mmol) was added dropwise to a solution of 2-(2-propynyl)phenol[6] (0.26 g, 2 mmol) in 2 mL of THF at 0 °C under a nitrogen atmosphere. To the reaction mixture was added a solution of $Pd(OAc)_2$ (45 mg, 0.2 mmol) and Ph_3P (53 mg, 0.2 mmol) in 1 mL of THF and then benzyl bromide (0.38 g, 2.2 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with water (10 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid, which was purified by HPLC (Chemcosorb 5-ODS-H, MeOH) to give (*E*)-2,3-dihydro-2-(2-phenylethylidene)-benzofuran[7] (0.29 g, 65%) as a white solid (mp 35–37 °C). The stereoisomeric purity was ≥98% as determined by GC and by ^1H NMR and ^{13}C NMR spectra. The relative stereochemistry of the vinyl proton and the benzylic protons was determined by ^1H-2D NOESY NMR spectrometry (entry 4).

Both acetylenic alkyl and aryl alkoxides undergo the cyclization and cross-coupling reaction to form five- or six-membered rings with high regio- and stereoselectivities. The palladium catalyst, Ph_3P, and *n*-BuLi are all essential to make the reaction take place.[8] Use of chloroform, dimethylformamide, toluene, or benzene as solvent gave only trace (<3%) or undetectable amounts of desired product. Using zinc alkoxide, prepared by treating a lithium alkoxide with 1 equiv of zinc chloride in THF, or coupling the acetylenic alkoxide with phenylzinc chloride in the reaction also gave no desired product. Both $Pd(OAc)_2$ and $PdCl_2$ were effective catalysts. Other palladium

(1) (a) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1187. (c) Luo, F. T.; Negishi, E. I. *J. Org. Chem.* **1983**, *48*, 5144. (d) Ley, S. V.; Lygo, B.; Organ, H. M.; Wonnacott, A. *Tetrahedron* **1985**, *41*, 3825.

(2) (a) Wang, R. T.; Chou, F. L.; Luo, F. T. *J. Org. Chem.* **1990**, *55*, 4846. (b) Luo, F. T.; Wang, R. T. *Heterocycles* **1990**, *31*, 1543 and 2181. (c) Luo, F. T.; Wang, R. T. *Heterocycles* **1991**, *32*, 2365.

(3) Luo, F. T.; Wang, R. T. *Tetrahedron Lett.* **1991**, *32*, 7703.

(4) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (c) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655. (d) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.

(5) The palladium-catalyzed cyclization of acetylenic carboxylates with allyl halides has been reported: Yanagihara, N.; Lambert, C.; Iritani, K.; Uitmoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753.

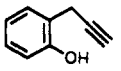
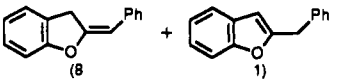
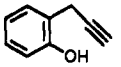
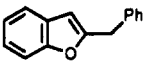
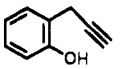
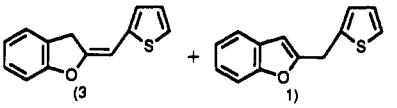
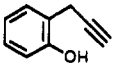
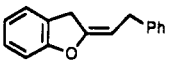
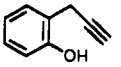
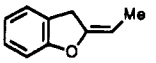
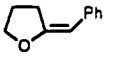
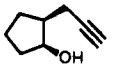
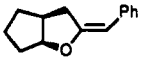
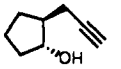
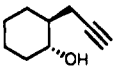
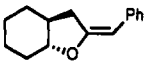
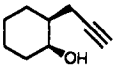
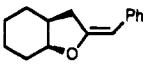
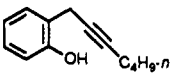
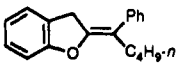
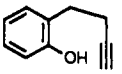
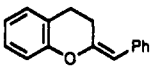
(6) Kall, T.; Sossi, Kh. *Uchenye Zapinski Tartusk. Gosudarst. Univ.* **1960**, *95*, 179; *Chem. Abstr.* **1962**, *56*, 5868d.

(7) All new compounds have been fully characterized by ^1H- and ^{13}C-NMR, MS or IR spectroscopy, and either elemental analysis or high-resolution mass spectroscopy. Although (*E*)-2-(phenylmethylene)tetrahydrofuran has been reported,[1d] we found that the reported NMR spectral data are different from ours (entry 6).

(8) The use of other bases, e.g., $NaHCO_3$, MeONa, in running the reaction gave no detectable amount of the desired product.

0022-3263/92/1957-2213$03.00/0

Table I. Intramolecular Cyclization and Cross-Coupling of Acetylenic Alcohols via Palladium Catalyst[a]

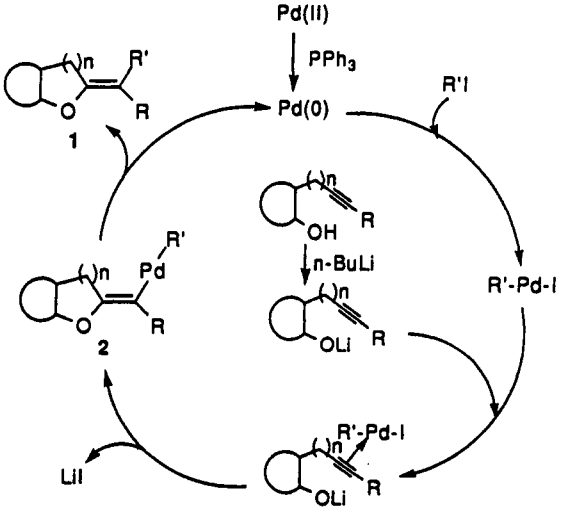
entry	substrate	Pd cat.	RX	product	isol. yield (%)
1		$PdCl_2$	PhI	 (8 : 1)	72
2		$Pd(PPh_3)_4$	PhI		28
3		$PdCl_2$		 (3 : 1)	75
4		$PdCl_2$	$PhCH_2Br$		65
5		$PdCl_2$	MeI		66
6		$Pd(OAc)_2$	PhI		53
7		$Pd(OAc)_2$	PhI		60
8		$Pd(OAc)_2$	PhI	–[a]	–[a]
9		$Pd(OAc)_2$	PhI		47
10		$Pd(OAc)_2$	PhI		54
11		$Pd(OAc)_2$	PhI		45
12		$Pd(OAc)_2$	PhI		48

[a] See text.

catalysts such as $Pd(dba)_2$ and $PdCl_2(PPh_3)_2$/DIBAL gave very low yields (<5%) of the desired product. $Pd(PPh_3)_4$ gave only the isomerized product 2-benzylbenzofuran[9] in low yield (entry 2). Probably the Pd(II) catalyst consumes the excess *n*-BuLi in the solution, lowering the basicity of the solution and minimizing double bond migration in the initial product; Pd(0) does not do this.[10]

Iodobenzene, benzyl bromide, iodomethane, and 2-iodothiophene all coupled with acetylenic alkoxides in the presence of palladium catalyst to form the exocyclic alkenes. When 2-(2-propynyl)phenol was reacted with iodobenzene or 2-iodothiophene, there was some migration of the double bond in the product (entries 1 and 3). On the other hand, no double-bond migration product was observed with the internal acetylene 2-(2-heptynyl)phenol (entry 11). When allyl chloride or *n*-butyl iodide was used in the coupling reaction, or when benzyl bromide was used in the absence of palladium catalyst, ethers were formed from the alkoxide and halide, and no cyclization occurred. While *cis*-2-(2-propynyl)cyclopentanol and *trans*- or *cis*-2-(2-propynyl)cyclohexanol afforded the desired alkenes in reasonable yields (entries 7, 9, 10), *trans*-2-(2-propynyl)cyclopentanol did not give any cyclized coupling product (entry 8) as judged from ^1H NMR.[11]

Scheme I. Possible Catalytic Cycle for Formation of 1 from Acetylenic Alcohols and Organic Halide in the Presence of Pd(II) Catalyst



This one-pot transformation probably involves sequential (1) proton abstraction from the alcohol, (2) complex-

(9) Kurosawa, K.; Morita, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 635.

(10) One of the reviewers commented that perhaps the number of phosphines released from $Pd(PPh_3)_n$ may be responsible for the double-bond migration.

(11) Oxymercuration[1a] and palladium-catalyzed cyclization[4a] of *trans*-2-(2-heptynyl)cyclopentanol has been reported to give a cyclic ether in 47–86% yields.

ation of the oxidative Pd(II) adduct with the triple bond followed by trans-oxypalladation to produce 2, and finally (3) reductive elimination to produce 1 and regenerate the palladium catalyst (Scheme I).

The facile hydrolysis[1a,12] of these exocyclic enol ethers in acid or even in dry chloroform-*d* can be prevented by adding 1–10% of Et_3N to their solutions.

Acknowledgment. We thank Academia Sinica and the National Science Council of the Republic of China for financial support.

Supplementary Material Available: Experimental section containing procedures and analytical data of starting materials and products (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) For example, *trans*-heptahydro-2(*E*)-(phenylmethylene)-2*H*-cyclohexa[*b*]furan is easily hydrolyzed to *trans*-2-(2-oxo-3-phenylpropyl)cyclohexanol in dry chloroform-*d* within 4 h at room temperature under nitrogen.

Controlled Molecular Aggregation. 1. Cyclic Trimerization via Hydrogen Bonding

Steven C. Zimmerman* and Brook F. Duerr

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

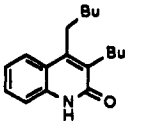
Received January 28, 1992

Summary: Vapor pressure osmometric and ^1H NMR dilution studies of quinolone **7**, isoquinolone **8**, and pyrido[4,3-*g*]quinolinedione **1**, indicate that **1** forms an extremely robust cyclic trimer in solution.

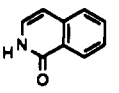
A contemporary challenge in organic chemistry is to develop strategies for controlling molecular aggregation.[1] In addition to providing insight into molecular recognition phenomena, advances in this area are likely to facilitate the creation of new materials and new molecular devices.[2] While numerous approaches to host–guest complexes have been developed, there are surprisingly few strategies available for forming mesomolecular aggregates (e.g., aggregates of 3–20 molecules). Such aggregates can be regarded as a logical first step toward engineering more complicated 3-dimensional assemblies with well-defined architectures. One potentially simple method for forming discrete mesomolecular aggregates in solution involves hydrogen bond mediated cyclic aggregation.[3,4] This strategy is illustrated by compound **1**, a pyrido[4,3-*g*]quinoline that was designed to form cyclic trimer **2** or linear aggregates (e.g., **3**) of any length, including dimers. Although **2** and **3** contain similar contacts, **2** is predicted to be of greater stability because it contains two hydrogen bonds per molecule of **1**, while **3** contains only $(2n + 2)/(n + 2)$ hydrogen bonds per **1**.[5] Herein we show that pyrido[4,3-*g*]quinolinedione **1** forms a robust aggregate in organic solvents and that the properties of the aggregate are consistent with those expected for cyclic trimer **2**.

Pyridoquinoline **1** was synthesized in nine steps as outlined in Scheme II.[6] Acylation of 3-bromoaniline by butyl ketene dimer[7] afforded keto amide **4**.[8] Knorr cyclization,[9] treatment with cuprous cyanide,[10] and DIBALH reduction gave quinolone **5**. Imine formation with aminoacetaldehyde dimethyl acetal and borohydride reduction afforded **6**,[11] which underwent oxidative cyclization with chlorosulfonic acid[12] and subsequent N-7 → C-8 oxidation[13] to form **1**.

The ability of **1** to aggregate in solution was examined both by ^1H NMR and vapor-pressure osmometry (VPO). The ^1H NMR spectra of **1** in chloroform-*d* was notable in that both N–H resonances appeared in the region (13–14 ppm) expected for fully associated (iso)quinolone systems. Furthermore, a striking difference in ^1H NMR dilution shifts was observed for **1** and model compounds **7** and **8**.



7



8

While the N–H chemical shifts of **1** were largely unchanged across a broad concentration range ($\Delta\delta < 0.3$ ppm), ca. 70% of the dilution curve could be observed for quinolone

(1) For leading references see: Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020. Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255. Schneider, H.-J.; Dürr, H., Eds. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; VCH: Weinheim, 1991.

(2) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304–1319. Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153–180.

(3) For designed systems see: Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787–5789. Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6409–6411. Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 712–713.

(4) This strategy may be applied to molecular and liquid crystal engineering: Desraju, G. R. *Crystal Engineering. The Design of Molecular Solids*; Elsevier: New York, 1989; Chapters 5 and 9. Eidenschink, R. *Angew. Chem., Int. Ed. Engl. Adv. Mat.* **1989**, *28*, 1424–1429. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126. Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696–4698. Bonazzi, S.; Capobianco, M.; De Morais, M. M.; Garbesi, A.; Gottarelli, G.; Mariani, P.; Bossi, M. G. P.; Spada, G. P.; Tondelli, L. *J. Am. Chem. Soc.* **1991**, *113*, 5809–5816 and references cited therein.

(5) If a cyclic aggregate contains *n* subunits, its advantage over the analogous linear aggregate will vanish as *n* becomes large.

(6) All new compounds gave correct elemental analysis and had spectroscopic data that were in accord with the reported structures. The (iso)quinolone tautomeric form for **1** and its aggregates is more probable than the hydroxy(iso)quinoline forms: Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186–192. Mirek, J.; Sygula, A. *Z. Naturforsch.* **1982**, *37a*, 1276–1283. Dyke, S. F.; Kinsman, R. G. In *The Chemistry of Heterocyclic Compounds: Isoquinolines*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, Part 1, p 11.

(7) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444–2448.

(8) Kaslow, C. E.; Cook, D. J. *J. Am. Chem. Soc.* **1945**, *67*, 1969–1972.

(9) For a review see: Jones, G. *The Chemistry of Heterocyclic Compounds*, Wiley: New York, 1977; Vol. 32; Part 1, pp 151–159.

(10) Cf. Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522–2524.

(11) Menon, C. S.; Zee-Cheng, R. K.-Y.; Cheng, C. C. *J. Heterocycl. Chem.* **1977**, *14*, 905–908.

(12) Kido, K.; Watanabe, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4964–4966 and references cited therein. Pomerantz–Fritsch-type cyclizations: Gensler, W. J. *Organic Reactions*; Wiley: New York, 1951; Vol. 6, pp 191–206.

(13) Robison, M. M.; Robison, B. L. *J. Org. Chem.* **1957**, *21*, 1337–1341. Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1958**, *80*, 3443–3449.

0022-3263/92/1957-2215$03.00/0